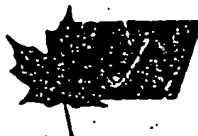


OPIC
OFFICE DE LA PROPRIÉTÉ
INTELLECTUELLE DU CANADA



Office: Hull K1A 0C9

CIPO
CANADIAN INTELLECTUAL
PROPERTY OFFICE

(21) (A1)	2,126,685
(82)	1993/10/18
(43)	1994/05/11

(51) INTL.CL.⁵ B01J-013/02; B01J-013/12; A61K-009/50; A61K-009/16

(19) (CA) APPLICATION FOR CANADIAN PATENT (12)

(54) Process for the Production of Microcapsules

(72) Gander, Bruno - Switzerland ;
Merkle, Hans P. - Switzerland ;

(71) Schwarz Pharma AG - Germany (Federal Republic of) ;

(30) (CH) 3319/92-3 1992/10/26

(57) 36 Claims

BEST AVAILABLE COPY

Notice: This application is as filed and may therefore contain an
incomplete specification.



Industrie Canada Industry Canada

3488

Canada

**PCT**WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales BüroINTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 5 : B01J 13/02, 13/12, A61K 9/16 A61K 9/50 2126685		A1	(11) Internationale Veröffentlichungsnummer: WO 94/03898 (43) Internationales Veröffentlichungsdatum: 11. Mai 1994 (11.05.94)
(21) Internationales Aktezeichen: PCT/CH93/00246 (22) Internationales Anmeldedatum: 18. Oktober 1993 (18.10.93) (30) Prioritätsdaten: 3319/92-3 26. Oktober 1992 (26.10.92) CH (71) Anmelder (für alle Bestimmungstaaten ausser US): SCHWARZ PHARMA AG (DE/DE); Alfred-Nobel-Strasse 10, D-40789 Monheim (DE). (72) Erfinder: und (75) Erfinder/Anmelder (nur für US): GANDER, Bruno (CH/CH); Eichlistrasse 21, CH-6405 Immensee (CH). MERKLE, Hans, Peter (DE/CH); Ottenbergstrasse 20, CH-8049 Zürich (CH). (74) Anwalt: GESELLSCHAFT ZUR FÖRDERUNG DER INDUSTRIEORIENTIERTEN FORSCHUNG AN DEN SCHWEIZERISCHEN HOCHSCHULEN UND WEITEREN INSTITUTIONEN (GFF); Technopark, Pfingstweidstrasse 30, CH-8005 Zürich (CH).		(81) Bestimmungstaaten: CA, FI, HU, JP, KR, US, europäisches Patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Veröffentlicht Mit internationalem Recherchenbericht.	
(54) Title: METHOD OF MANUFACTURING MICROCAPSULES (54) Bezeichnung: VERFAHREN ZUR HERSTELLUNG VON MIKROKAPSELN (57) Abstract Described is a method of manufacturing microcapsules from biodegradable polymers, the method using biodegradable solvents and producing microcapsules which are free from toxic solvent residues. The solvents used include simple esters made from a C ₁ -C ₃ alcohol and a C ₁ -C ₃ monocarboxylic acid, as well as mixtures of such esters, and the solvent can also contain a C ₁ -C ₃ alcohol. Both water-soluble and water-insoluble active substances can be incorporated in the microcapsules. Water-soluble active substances such as drugs, peptides, proteins, enzymes and vaccines are preferably dispersed as an aqueous solution in the polymer solution. The microcapsules are produced by spraying a solution, suspension or water-in-oil dispersion of active substances and biodegradable polymers. The method is suitable for use in the manufacture of drug, vaccine and enzyme preparations. (57) Zusammenfassung Es wird ein Verfahren zur Herstellung von Mikrokapseln, ausgehend von bioabbaubaren Polymeren, beschrieben, welches biologisch abbaubare Lösungsmittel verwendet, und Mikrokapseln frei von toxischen Restlösungsmitteln liefert. Die verwendeten Lösungsmittel umfassen einfache Ester, aufgebaut aus einem C ₁ -C ₃ -Alkohol und einer C ₁ -C ₃ -Monocarbonsäure, sowie aus Gemischen dieser Ester, wobei dieses Lösungsmittel zusätzlich einen C ₁ -C ₃ -Alkohol enthalten kann. Als einzubettende Wirkstoffe werden sowohl wasserlösliche wie auch wasserunlösliche Substanzen verwendet. Wasserlösliche Wirkstoffe wie Arzneistoffe, Peptide, Proteine, Enzyme und Impfstoffe werden vorzugsweise als wässrige Lösung in der Polymerlösung dispergiert. Die Mikrokapseln werden durch Versprühen einer Lösung, Suspension oder W/O-Dispersion aus Wirkstoffen und bioabbaubaren Polymeren erhalten. Das Verfahren findet Anwendung in der Herstellung von Arzneistoff-, Impfstoff- und Enzymzubereitungen.			

2126685

4139.2-US-WO

PATENT

PROCESS FOR THE PRODUCTION OF MICROCAPSULES

FIELD OF THE INVENTION

The present invention concerns a process for the
5 production of biodegradable microcapsules employing
biodegradable and toxicologically harmless solvents. The
term, microcapsule, used, for simplicity's sake, includes
actual microcapsules as well as microspheres and
microparticles according to the following definitions: The
10 term microcapsule describes spherical particles in the size
range 1-1,000 μm , consisting of an internal nucleus, which
contains the active material in liquid or solid form, and
the capsule wall consisting of polymer. The terms
15 microspheres or microparticles describe spherical and non-
spherical particles in the size range of
1-1,000 μm , consisting of a polymer matrix, in which the
active material is imbedded as a so-called solid solution
or suspension.

BACKGROUND OF THE INVENTION

20 Biologically highly sensitive active materials such as
certain pharmaceuticals, peptides, proteins, enzymes and
vaccines are preferably used parenterally as injection
solutions. Many of these active materials have a short
biological half-life or are not very active when applied in
25 solution (vaccines). This means, that a continuous or
pulse-like release of active material (long term release)
represents an unavoidable prerequisite for a successful
therapeutic or preventive treatment. Such prolonged
release of active material can be achieved through
30 incorporating the active material, for example, into a
biodegradable release system. Such release systems can be
produced in the form of microcapsules or implant rods.

2126685

Biodegradable microcapsules have proved to be especially useful in the past, because these particles can be easily administered parenterally with common injection needles.

Known biodegradable pharmaceutical release systems are

- 5 based on polyesters of lactic acid and glycolic acid (D. H. Lewis, Controlled release of bioactive agents from lactide/glycolide polymers, in: Biodegradable polymers as drug delivery systems, M. Chasin, and R. Langer (Eds.), M. Dekker, New York, 1990, pp. 1-41).

- 10 For the production of microcapsules from polyesters, such as poly(lactides) and poly(lactide-co-glycolides), three main processes are known: the coacervation (phase separation), e.g. through addition of a non-solvent, solvent evaporation, or solvent extraction from an oil-in-
15 water dispersion, and spray drying (R. Jalil et al., J. of Micro-encapsulation 7,297-325, (1990)). Common to all of these processes is the requirement of an organic polymer solvent, which is removed again for the most part through the process. Because the complete removal of the solvent
20 from the polymer is not possible, residual solvent always remains in the microcapsules, lying in the range of 0.01-10% (G. Spenlehauer et al., Biomaterials 10, 557-563, (1989)); D. H. Lewis et al., PCT WO 89/03678). The solvents mainly described until now for the three processes
25 above are not biodegradable and in part are extremely toxic or environmentally harmful, e.g. methylene chloride, chloroform, benzene, tetrahydrofuran, acetonitrile, fluorochlorohydrocarbons and others, which compromise the advantages of these biodegradable release systems.

- 30 For illustration, according to the U.S. Patent 5,066,436 microcapsules are produced through coacervation, which are contaminated with such organic solvents to a large extent. In addition to the polymer solvent, other

2126685

organic solvents are used for the actual phase separation, for the hardening and washing of the microcapsules. Moreover, the microcapsules produced this way are relatively large and agglomerate easily during the
5 production process which additionally aggravates the removal of residual solvent.

The disadvantages connected with the solvent evaporation or extraction methods lie in the previously mentioned toxicologically not completely harmless residual
10 solvents of the microcapsules. On the other hand, these particular methods show the inherent difficulty that water soluble active materials such as certain pharmaceuticals, peptides, proteins, enzymes, and vaccines are lost through the aqueous dispersion phase and, therefore, escape partial
15 or complete encapsulation.

Spray drying is a known, simple and quick process for the production of biodegradable microcapsules. The difficulty of producing spherical and not porous particles of the biodegradable lactic and glycolic acid polymers has
20 been repeatedly pointed out. With the poly (D,L-lactic acid) dissolved in methylene chloride, very irregular microcapsules are obtained with an irregular surface and a high proportion of fibrous material (R. Bodmeier et al., J. Pharm. Pharmacol. 40, 754-757 (1988)). According to the
25 European Patent Application A1 315,875 copolymers of lactic and glycolic acid (PLGA) cannot be processed into microcapsules via spray drying. These copolymers are, however especially interesting as matrix or wall material, because they break down more quickly in the organism than
30 the pure homopolymers of lactic and glycolic acid. It has been described that the PLGA-polymers, especially PLGA composed of 50% of each lactic and glycolic acid (PLGA 50:50), give release of the active material over 3-4 weeks,

2126685

which for example for hormonal and enzyme therapy represents a desirable dosing interval.

A further difficulty with spray drying for microencapsulation arises from the properties of the substance to be encapsulated. Substances, which are soluble in polymer solution (e.g. in methylene chloride), are usually built into microcapsules with relatively high efficiency and homogenous distribution (high 'content uniformity'). In contrast, the microencapsulation of substances which are insoluble in polymer solution is more difficult as for example for certain pharmaceuticals, peptides, proteins, enzymes and vaccines. If these active materials are suspended in the organic polymer solution in a micronized form, only an unsatisfactory incorporation efficiency is often achieved, which is strongly dependent on the fineness of the active material. For this reason, water soluble active materials are often first dissolved in water, and the aqueous solution of active material solution is then dispersed in the polymer solution (water-in-oil dispersion). With the common known solvents, only unsatisfactory water-in-oil dispersions can be produced which prove to have insufficient fineness and physical stability. The result is a quick coalescence of the dispersed, aqueous phase (coalescence), and connected with this, a poor encapsulation efficiency. For this reason, it has been repeatedly observed that micro-encapsulated protein is released within 1-3 days. This is traced back in general to a high proportion of insufficiently encapsulated active material and high microcapsule porosity (H. T. Wang et al., Biomaterials, 11, 679-685 (1990)). In addition, water miscible solvents such as acetone, tetrahydrofuran, dioxane, acetonitrile and other cannot be

2126685

used because this miscibility may lead to precipitation or aggregation of the active material and/or the polymer.

SUMMARY OF THE INVENTION

The present invention solves the above problems by
5 manufacturing microcapsules using a method which employs biodegradable and toxic-free materials.

Accordingly, the present invention is a method of manufacturing microcapsules containing one or more biodegradable polymers and at least one active material,
10 which method comprises:

- (a) dissolving the biodegradable polymer(s) in a biodegradable solvent;
- (b) mixing the active material in a biodegradable solvent or aqueous medium;
- 15 (c) combining components (a) and (b), and
- (d) spray drying the resulting mixture.

Essential to the invention is the use of biodegradable solvents, whereby the microcapsules manufactured with them are free of toxic residual solvents. The microcapsules are
20 obtained by spraying of a solution, suspension or dispersion of active materials and polymers. Water soluble as well as water insoluble biologically active substances are suitable for active materials to be imbedded. Water soluble active materials like peptides, proteins, vaccines
25 preferably are dispersed as aqueous solutions in the polymer solution. Hereby a process is available, which is applicable in the production of pharmaceutical, vaccine and enzyme preparations.

BRIEF DESCRIPTION OF THE DRAWING

30 Figure 1 shows the flow diagram for a process for the production of microcapsules of the present invention.

2126685

DETAILED DESCRIPTION

The following is a detailed description of the embodiments of the present invention including a best mode. Each operation is separately described as shown in Figure

5 1.

1. Dissolving (I)

Starting point for the process are all biodegradable polymers, as far as they are soluble in the solvents according to the invention, like mono- and co-
10 polyesters of the lactic, glycolic, and β -hydroxybutyric acids, as well as δ -valerolactone and ϵ -caprolactones. Polylactic and polyglycolic acid are also termed poly (lactides) and poly (glycolides). The dissolving of biodegradable polymers, or a mixture of biodegradable
15 polymers, takes place in the solvents according to the invention, whereby a polymer solution (first solution) is generated. To these solvents belong the group of simple esters, consisting of a C_1 - C_3 alcohol and a C_1 - C_3 monocarboxylic acid, and mixtures of these simple esters
20 with a C_1 - C_3 -alcohol. To these biodegradable solvents belong for example ethyl formate, propyl formate, butyl formate, ethyl acetate, propyl acetate, isopropyl acetate, ethyl propionate, ethyl butyrate, and ethyl valerate, and mixtures of these esters with ethanol, propanol,
25 isopropanol and others. These solvents or solvent mixtures possess a surprisingly high solubility for biodegradable polyesters made, for example, of glycolic acid, lactic acid β -hydroxybutyric acid, δ -valerolactone and of ϵ -caprolactone. They are able to dissolve homopolymers as
30 well as copolymers of these hydroxycarboxylic acids in a wide variation of molar ratios, for example 50:50, 65:35, 75:25 or 85:15, and over a wide range of molecular weights (2,000-150,000). The polymers can be brought into solution

2126685

individually or as a mixture and the solvents according to the invention may be used individually or as solvent mixtures, made up of different esters or of esters and alcohols.

5 2. Embedding of the active material

The embedding of the active material to be encapsulated into the biodegradable polymer occurs in dependence of the active material's solubility in three different ways, corresponding to steps 3, 5 and 6.

10 According to this invention, active materials are defined as substances which in living organisms, produce a biological effect, whereby this effect, for example, can be a pharmacological, an immunological, or enzymatic one. The active material to be encapsulated, in general, is in solid
15 form (powder) but can also be in liquid form and can be processed as a liquid.

3. Dissolving (II)

Active materials, which are soluble in the biodegradable solvents according to the invention,
20 consisting of esters, C₁-C₈-alcohols and any ester-alcohol mixture of these, are directly dissolved in these whereby an organic active material solution (second solution) is generated. This active material solution represents the preferred process step, because it can be manufactured with
25 the least effort and is thermodynamically stable.

4. Mixing

Subsequently the polymer solution (first solution) and the organic active material solution (second solution) are combined and mixed, whereby the substrate 'solution' is
30 obtained. The solvents described here are characterized by a high solubility for a large number of low-molecular active materials; like certain pharmaceuticals and peptides. This advantageous property of these solvents

2126685

also makes it possible to dissolve the active material and the biodegradable polymer simultaneously, by using the same solvent or a combination of biodegradable solvents. The process is then continued with step 8.

5 5. Suspending

Active materials, which are neither sufficiently soluble in water nor in the solvents according to the invention, are suspended mechanically or by means of ultrasound in the polymer solution, which contains the biodegradable solvents, whereby the substrate 'suspension' is obtained. To achieve a high incorporation efficiency, the active material is preferably suspended in a micronized form. Thereby, in general particles smaller than 10 μm are generally strived for. The process is then continued with step 8.

6. Dissolving (III)

Water-soluble active materials, like certain pharmaceuticals, peptides, proteins, enzymes, or vaccines, which cannot be dissolved in the solvents according to the invention, are preferably dissolved in an aqueous medium with as small a volume as possible, whereby an aqueous active material solution is generated. The aqueous medium can contain additives, as for example buffer salts, tensides, stabilizers and preservatives.

25 7. Dispersing

The aqueous active material solution obtained in step 6 subsequently is finely dispersed in the polymer solution, which contains the biodegradable polymer in the solvents according to the invention, whereby the substrate water-in-oil (W/O) dispersion is obtained. In this way, aqueous active material solutions up to a volume of 50% can be incorporated nanodispersedly into the polymer solution with little energy input. The dispersion can take place by

2126685

means of simple shaking, but preferably by means of a mechanical dispersion tool or with ultrasound. The preferred dispersion method is ultrasound treatment with 50-400 W during 10-300 s or longer if necessary. These
5 dispersions of aqueous active material solutions in polymer solution remain surprisingly stable over several hours (no coalescence) without addition of surfactants or pseudoemulsifiers and do not have to be continually dispersed during the spraying process, which is especially
10 advantageous. The solvents according to the invention yield W/O-dispersions with aqueous active material solutions, which, with regards to fineness and stability, cannot be achieved with the solvents commonly used, as for example methylene chloride. The process is continued in
15 step 8.

8. Spray Drying

The substrates obtained in steps 4, 5 and 7 'solvent', 'suspension' and 'W/O-dispersions' respectfully, are processed into microcapsules by spray drying which, for
20 example, can take place with a Mini Spray Dryer 190 (Büchi). Microcapsules manufactured by spray drying generally have a diameter of 1-50 μm , but maximally 100 μm , and thus can easily pass through an injection needle. The degree of loading of the microcapsules (active material
25 content) is between 0-50%, but preferably between 0-20%.

Microcapsules manufactured in this way are processed further in the appropriate manner and in accordance with the final use where for example a washing process, a fractionation into different particle sizes, a final drying
30 under high-vacuum, a sterilization by means of γ -radiation or further processing can follow as desired.

2126685

The process described here in steps 1-8 allows to encapsulate active materials with differing solubility characteristics of a high incorporation efficiency and with a homogenous distribution in the polymer, because of the high dissolving capability of the solvents according to the invention for many active materials and because of the simple dispersibility of aqueous active material solutions. Depending on the polymer used, the degree of loading and the use of additives (release regulators), the active material is released from the microcapsule over a time period from 1 day to 1 year.

In contrast to the commonly used halogenated and non-halogenated organic solvents, the biodegradable solvents enable to produce microcapsules by spray drying even with poly (D,L-lactic acid) or poly (lactic-co-glycolic acid). The obtained products exhibit a regular spherical particle morphology and a smooth non-porous surface. Particle conglutination, agglomeration, or deformation are seldom seen.

The solvents according to the invention have, in addition, the extraordinary advantage that they are toxicologically harmless. Just as the polymers, which are the basis of the microcapsules, the solvents according to the invention, break down in the organism into smaller, non-toxic, and in part physiological components. This decomposition occurs mainly through hydrolysis, but can also be enzymatic, for example occurring by means of esterases or dehydrogenases. Contrary to the solvents according to the invention, the commonly employed solvents are transformed in the organism into toxic metabolites. Methylene chloride, for example, is metabolized in the organism into the respiratory poison carbon monoxide and

2126685

into compounds with carcinogenic potential and varying toxicological effects.

The following list is illustrative but not exhaustive of the active materials which may be contained in the biodegradable microcapsules prepared by the present invention:

- A. Low molecular weight active materials such as psychotropics, neuroleptics, e.g. promethazine, promazine, chlorpromazine, trifluorpromazine, alimemazine, levomepromazine, thioridazine, sulforidazine, periciazine, perazine, trifluoperazine, perphenazine, fluphenazine, dixyrazine, prothipendyl, chlorprothixen, clopenthixol, flupentixol, melperone, haloperidol, bromperidol, trifluoperidol, pipamperone, benperidol, fluspirilen, pimozide, sulpiride; antidepressants, (monoamine oxidase (MAO) inhibitors), e.g. imipramine, desipramine, trimipramine, lofepramine, clomipramine, opipramol, amitriptyline/-oxide, nortriptyline, protriptyline, dibenzepine, doxepin, melitracen, mianserin, maprotilin, (nomifensin), trazodone, viloxazin; tranquilizers (therapeutic use: as anxiolytic sedatives), e.g. (-meprobamate), benzodiazepine, e.g. diazepam, prazepam, oxazepam, lorazepam, clonazepam, bromazepam, alprazolam; nootropic drugs, e.g. piracetam, pyritinol, meclofenoxate; opioid antagonists, e.g. naloxone, nalorphin, levallorphan, and opioid analgesics, e.g. morphine, hydromorphone, oxycodone, pethidin, levomethandone, dextromoramide, pentazoxine, buprenorphin, tilidine, tramadol, fentanyl, alfentanil.
- B. Nonsteroidal antiinflammatory drugs (NSAID) therapeutic use: rheumatic diseases, e.g. indomethacin, acemetacin, sulindac, tolmetin, diclofenac, lonazolac, ibuprofen, flurbiprofen, fenoprofen, ketoprofen, naproxen,

2126685

- pirprofen, indoprofen, carprofen, thiaprofen carboxylic acid, piroxicam, isoxicam; antiepileptics, e.g. phenobarbital, primidone, phenytoin, ethosuccimide, carbamazepine, valproic acid; antiparkinson drugs, e.g.
- 5 amantadine, benserazide, l-dopa, carbidopa, selegilin, biperiden, metixen, trihexyphenidyl; beta blockers, e.g. bupranolol, alprenolol, oxprenolol, penbutolol, metoprolol, betaxolol, atenolol, acebutolol, metipranolol, propranolol, nadolol, pindolol, mepindilol, bopindolol, carteolol,
- 10 carazolol, timolol, sotalol, toliprolol; calcium channel blockers, e.g. isradipine, nifedipine, nitrendipine, nimodipine, verapamil, gallopamil, diltiazem, prenylamine, fendiline, flunarizine; angiotensin converting enzyme (ACE) inhibitors, e.g. captopril, moexipril, enalapril,
- 15 fosinopril, ramipril, perindopril, lisinopril, quinapril; nitrates, e.g. ISDN, 5-ISM, pentaerythrityltetranitrate, GTN; vasodilators, e.g. pentoxifylline, cinnarizine, bencyclan; prolactin inhibitors, e.g. bromocriptin, lisuride, metergoline, thyroid hormones, e.g. levothyroxine
- 20 (T_4), liothyronin (T_3), and oral antidiabetics, e.g. carbutamide, tolbutamide, chlorpropamide, glymidine, glibornuride, glibenclamide, glipizide, gliquidone, glisoxepid.

- C. Sex hormones (female/male)/anabolic
- 25 steroids/hormone antagonists, e.g. estradiol, estradiolvalerate, estradiolbenzoate, estradiolcypionate, estradioldienatate, estradioldipropionate, estradiolenantate, estradiolphenylpropionate, estradiolpivalate, estradiolundecylenate, ethinylestradiol,
- 30 estriol, mestranol, quinestrol, diethylstilbestrol, progesterone, norethindrone, desogestrel, dienogest, levonorgestrel, norgestrel, chlormadinone acetate, lynestrenol, allylestrenol, ethynodiol diacetate,

2126685

- medroxyprogesterone acetate, hydroxyprogesterone acetate, testosterone, testosterone propionate, testosterone undecanoate, meserolone, e.g. nandrolone decanoate, clostebol acetate, metenolone acetate, stanozolol, e.g.
- 5 cyproterone acetate, flutamide, drostanolone propionate, testolactone, clomifen, cyclofenil, tamoxifen, estramustin, fosfestrol, chlorotrianisen, aminoglutethimide.
- D. Antihistamines (as depot antiallergic agent for example for hay fever), e.g. terfenadine, astemizol,
- 10 dimetinden, clemastin, pheniramine, dexchlorpheniramine, azatadine, oxatamide; serotonin antagonists, e.g. methysergide, cyproheptadine, pizotifen, ketanserin; prostaglandins/prostacyclin, e.g. PGE1/2, PGF 2a, prostacycline; anticoagulants, e.g. acenocoumarol,
- 15 phenprocoumone, warfarin, ASS; blood lipid regulating drugs, e.g. clofibrate, etofibrate, bezafibrate, fenofibrate, gemfibrozil, lovastatin, pravastatin; vitamins (fat-soluble, water-soluble), e.g. Vit. A, Vit. D, Vit. E, (-Vit. K), Vit. B1, Vit. B2, Vit. B6, Vit. B12, Vit. Bc,
- 20 Vit. C, biotin; chemotherapeutic agents/antibiotics (sulfonamide/combinations, β -lactams, tetracycline, macrolide, aminoglycoside), e.g. sulfacarbamide, sulfafurazol, sulfisomidine, sulfadiazine/(tetroxoprim), sulfamethoxazol/(trimethoprim), sulfamethoxypyridazine,
- 25 sulfamethoxydiazine, sulfaperin, sulfadimethoxin, sulfamethoxypyrazine, sulfaguanol, e.g. nalidixic acid, oxalinic acid, quinoxalinic acid, pipemidic acid, norfloxacin, ofloxacin, ciprofloxacin, benzylpenicillin, phenoxymethylpenicillin, propicillin, oxacillin,
- 30 dicloxacillin, flucloxacillin, ampicillin, amoxicillin, epicillin, azlocillin, methacillin, piperacillin, apalcillin, carbenicillin, ticarcillin, temocillin, bacampicillin, cephalothin, cefaloridine, cefazoline,

2126685

- cefazedone, cefamandole, cefuroxime, cefotiam, cefoxitin, cefotetan, cefotaxime, ceftizoxime, cefmenoxime, ceftriaxone, ceftazidime, cefoperazone, cefsulodin, cephalixin, cefaclor, cefradine, cefadroxil, latamoxef,
- 5 aztreonam, imipenem, cilastatin, tetracycline, oxytetracycline, demeclocycline, doxycycline, minocycline, rolitetracycline, erythromycin, streptomycin, clindamycin, neomycin, kanamycin A; antifungal agents, e.g. griseofulvin, amphotericin, ketoconazol, miconazol;
- 10 chemotherapeutic agents (antimetabolites, antibiotics, hormone antagonists, sex hormones), e.g. methotrexate, mercaptopurine, fluorouracil, cytarabine, aclarubicin, daunorubicin, doxorubicin, dactinomycin, epirubicin, bleomycin; high molecular weight active materials, e.g.
- 15 erythropoietin, LH-RH-analogs, nafarelin, triptorelin, leuporelin, buserelin, goserelin, antide, ciclosporin (A), interferon, somatotropin, somatostatin and analogs, octreotide, lanreotide, vapreotide, calcitonin, CGRP (calcitonin gene related peptide), ANP (atrial natriuretic peptide), BNP (brain natriuretic peptide), EGF (epidermal growth factor), GLP (glucagon like peptide), heparin, hirudin, hirugen, superoxide dismutase, angiotensinase, medullipin II, HBGF1 (KHK); endorphins/enkephalins, e.g. α, β, γ -endorphin, dynorphin, met-enkephalin, leu-enkephalin,
- 20 and vaccines, e.g. tetanus-toxoid-vaccine, diphtheria-toxoid vaccine, influenza, hepatitis, poliomyelitis, measles, mumps, German measles, pertussis, FSME, cholera, typhus-/paratyphus, and rabies.

- 30 The following are specific examples to illustrate the present invention and are not limiting thereon.

EXAMPLE 1

The production of microcapsules, containing a protein: 0.09 g bovine serum albumin (Fluka, CH-Buchs) have been

2126685

dissolved in 2.16 g water. With the help of an ultrasonic generator the aqueous solution was dispersed in a solution of 3.0 g Poly(D,L-lactic acid)(Resomer R202, Boehringer Ingelheim) in 57.0 g propyl acetate. The dispersion took
5 place under cooling with ice in an ultrasonic processor (Vibracell, VC375, Sonics and Materials, Danbury, CT) with an energy of 260 W during 2 x 30 s. This dispersion was sprayed in a laboratory spray dryer (Mini Spray Dryer, Büchi 190, Büchi Laboratories, CH-Flavil) under the
10 following conditions: Inlet temperature: 55°C, spray flow: 400 scale units, aspirator: 15 scale units, spray speed: 2.4 ml/min.

The microcapsules arose as a white, free-flowing powder. Yield: 1.8 g (58% of the theoretical value),
15 active material content: 2.9% (100% of the theoretical value).

EXAMPLE 2

The production of microcapsules, containing a protein:
0.09 g Bovine serum albumin were dissolved in 2.16 g water.
20 The aqueous solution was dispersed with the aid of an ultrasonic generator (260 W during 30 s) in a solution of 3.0 g Poly(D,L-lactic acid) (Resomer R202, Boehringer Ingelheim) in 57.0 g ethyl acetate. Dispersion and spray drying took place under identical conditions as in Example
25 1. Yield: 1.6 g (52% of the theoretical value), active material: 2.9% (100% of the theoretical value).

EXAMPLE 3

The production of microcapsules, containing a vaccine:
0.100 g lyophilized tetanus toxoid was dissolved in 2.0 ml
30 water. The aqueous solution was dispersed with the aid of an ultrasonic generator in a solution of 5.0 g Poly(D,L-lactic acid-co-glycolic acid)(Resomer RG502, Boehringer

2126685

Ingelheim) in 100.0 g ethyl ester. The dispersion took place under ice cooling with an ultrasound energy of 210 W during 2 x 30 s. The dispersion was sprayed in a laboratory spray dryer under the following conditions:

- 5 Inlet temperature: 55°C, spray flow: 500 scale units, aspirator: 17.5 scale units, spray speed: 2.4 ml/min.

The microcapsules arose as a white, free-flowing powder. Yield: 0.7 g (40% of the theoretical value), protein contents: 1.82%, equivalent to 93% of the
10 theoretically determined active material contents.

EXAMPLE 4

The production of microcapsules, containing an enzyme: 15 mg peroxidase from horse-radish with an activity of 75.8 U/mg (Fluka, CH-Buchs) were dissolved in 0.6 ml water. The
15 aqueous solution was dispersed by means of ultrasonics of 375 W during 30 s under cooling with ice in a solution of 1.5 g Poly(D,L-lactic acid)(Resomer R202, Boehringer Ingelheim) in 30.0 g ethyl formate. The dispersion was sprayed with a laboratory spray dryer under the following
20 conditions: Inlet temperature: 47°C, spray flow: 450 scale units, aspirator: 17 scale units, spray speed: 1.6 ml/min.

The microcapsules arose as a white, free-flowing powder. Yield: 0.92 g (61% of the theoretical value),
25 enzyme activity: 0.177 U/mg microcapsules, corresponding to 23.4% of the theoretically determined activity.

EXAMPLE 5

The production of microcapsules, containing a pharmaceutical: 30 mg prostaglandin E2 (Fluka, CH-Buchs)
30 and 6.0 g poly(D,L-lactic acid-co-glycolic acid)(Resomer RG502, Boehringer Ingelheim) were dissolved separately in 60 g ethyl formate each. The combined solutions were sprayed under the following conditions: Inlet temperature:

2126685

45°C, spray flow: 420 scale units, aspirator: 15 scale units, spray speed: 2.4 ml/min.

The microcapsules arose as a white, free-flowing powder. Yield: 4.2 g (70% of the theoretical value),
5 degree of loading: 4.99 µg/mg microcapsules (100% of theoretical value).

EXAMPLE 6

The production of microcapsules, containing a hormone:
25 g 17-beta-estradiol were dissolved in a mixture of 125
10 ml anhydrous ethanol and 312.5 ml ethyl acetate. 100 g Resomer RG503 (Boehringer Ingelheim) were dissolved in 812.5 ml ethyl formate. Both solutions were combined under stirring whereby a stable suspension was formed.

The suspension was sprayed in a mobile Minor Spray
15 Dryer (Company MIRO AS, Copenhagen): Inlet temperature: 67°C, spray speed: 0.9 l/h.

The microcapsules arose as a white powder, containing discrete, spherical particles. Yield: 80 g (80% of the theoretical value); degree of loading: 70.2 µg/mg
20 microcapsules (85.1% of the theoretical value).

EXAMPLE 7

The production of microcapsules containing a hormone:
10 g 17-beta-estradiol were dissolved in a mixture of 100
25 ml anhydrous ethanol and 250 ml ethyl acetate. 20 g Resomer RG752 (Boehringer Ingelheim) were dissolved in 650 ml ethyl formate. The two solutions were combined under stirring and sprayed in a mobile Minor Spray Dryer (Company MIRO AS, Copenhagen) under the following conditions: Inlet temperature: 70°C, spray speed: 0.9 l/h.

30 The microcapsules arose as a white powder, containing discrete, spherical particles. Yield: 100 g (85% of the theoretical value); degree of loading: 89.6 µg/mg microcapsules (89.6% of the theoretical value).

2126685

EXAMPLE 8

The production of microcapsules, containing a synthetic vaccine: 0.02 g of a synthetic protein, consisting of the peptide sequence 947-967 of the tetanus toxin and a B-cell epitope of the repetitive region of the circumsporozoite protein of *Plasmodium berghei*, were dissolved in water. The aqueous solution was dispersed with the aid of an ultrasonic generator in a solution of 2.0 g Poly(D,L-lactic acid-co-glycolic acid) (Resomer RG752, Boehringer Ingelheim) in 40.0 g ethyl formate. The dispersion took place under cooling with ice with an ultrasound energy of 210 W during 2 x 30 s. The dispersion was sprayed in a laboratory spray dryer under the following conditions: Inlet temperature: 50°C, spray flow: 450 scale units, aspirator: 14 scale units, spray speed: 2.6 ml/min.

The microcapsules arose as white, free-flowing powder. Yield: 1.12 g (56% of the theoretical value); protein contents: 0.66%, corresponding to 0.6% of the theoretically determined active material content.

2126685

WHAT IS CLAIMED IS:

1. A method of manufacturing microcapsules containing one or more biodegradable polymers and at least one active material, which method comprises:
 - 5 (a) dissolving the biodegradable polymer(s) in a biodegradable solvent;
 - (b) mixing the active materials in a biodegradable solvent, an aqueous medium or in (a);
 - 10 (c) combining components (a) and (b), and
 - (d) spray drying the resulting mixture.
2. The method of Claim 1, wherein the biodegradable solvent is a simple ester or a mixture of a simple ester with a C₁-C₃-alcohol.
- 15 3. The method of Claim 1, wherein the biodegradable solvent is a simple ester.
4. The method of Claim 3, wherein the simple ester consists of a C₁-C₃-alcohol and a C₁-C₃-monocarboxylic acid.
5. The method of Claim 1, wherein the biodegradable solvent is ethyl formate.
- 20 6. The method of Claim 1, wherein the biodegradable solvent is ethyl acetate.
7. The method of Claim 1, wherein the biodegradable solvent is isopropyl acetate.
- 25 8. The method of Claim 1, wherein the active material is a biologically active substance.
9. The method of Claim 8, wherein the biologically active substance is a pharmaceutical, a peptide, a protein, an enzyme or a vaccine.
- 30 10. The method of Claim 8, wherein the biologically active substance is a pharmaceutical, a vaccine or an enzyme.

2126685

11. A microcapsule containing one or more biodegradable polymers and a biologically active substance as prepared by the method of Claim 1.

12. The microcapsule of Claim 11, wherein the biologically active substance is selected from a pharmaceutical, a peptide, a protein, an enzyme and a vaccine.

13. The microcapsule of Claim 12, wherein the biologically active substance is a pharmaceutical, a vaccine or an enzyme.

14. A method of manufacturing microcapsules comprising:

- (a) dissolving one or more biodegradable polymers in a biodegradable solvent to form a first solution;
- (b) dissolving an active material in a biodegradable solvent to form a second solution;
- (c) combining the first solution with the second solution to obtain a substrate solution and,
- (d) spray drying the substrate solution.

15. The method of Claim 14, wherein the biodegradable solvent is a simple ester or a mixture of a simple ester with a C₁-C₃-alcohol.

16. The method of Claim 14, wherein the biodegradable solvent is a simple ester.

17. The method of Claim 16, wherein the simple ester consists of a C₁-C₃-alcohol and a C₁-C₃-monocarboxylic acid.

18. The method of Claim 14, wherein the biodegradable solvent is ethyl formate.

19. The method of Claim 14, wherein the biodegradable solvent is ethyl acetate.

2126685

20. The method of Claim 14, wherein the biodegradable solvent is isopropyl acetate.

21. A method of manufacturing microcapsules comprising:

- 5 (a) dissolving one or more biodegradable polymers in a biodegradable solvent to form a polymer solution;
- (b) suspending an active material mechanically or by means of ultrasound in the polymer solution to obtain a substrate suspension, and
- 10 (c) spray drying the substrate suspension.

22. The method of Claim 21, wherein the biodegradable solvent is a simple ester or a mixture of a simple ester with a C₁-C₃-alcohol.

23. The method of Claim 21, wherein the biodegradable solvent is a simple ester.

24. The method of Claim 23, wherein the simple ester consists of a C₁-C₃-alcohol and a C₁-C₃-monocarboxylic acid.

20 25. The method of Claim 21, wherein the biodegradable solvent is ethyl formate.

26. The method of Claim 21, wherein the biodegradable solvent is ethyl acetate.

25 27. The method of Claim 21, wherein the biodegradable solvent is isopropyl acetate.

28. The method of Claim 21, wherein the active material is in micronized form.

29. A method of manufacturing microcapsules comprising:

- 30 (a) dissolving one or more biodegradable polymers in a biodegradable solvent to form a polymer solution;

2126685

- (b) dissolving an active material in an aqueous medium to form an aqueous active material solution;
- (c) mixing the aqueous active material solution with the polymer solution mechanically or with ultrasound to obtain a substrate water-in-oil dispersion, and
- (d) spray drying the substrate water-in-oil dispersion.
- 10 30. The method of Claim 29, wherein the biodegradable solvent is a simple ester or a mixture of a simple ester with a C₁-C₃-alcohol.
31. The method of Claim 29, wherein the biodegradable solvent is a simple ester.
- 15 32. The method of Claim 31, wherein the simple ester consists of a C₁-C₃-alcohol and a C₁-C₃-monocarboxylic acid.
33. The method of Claim 29, wherein the biodegradable solvent is ethyl formate.
34. The method of Claim 29, wherein the biodegradable solvent is ethyl acetate.
- 20 35. The method of Claim 29, wherein the biodegradable solvent is isopropyl acetate.
36. The method of Claim 29, wherein the dispersion in step (c) is obtained with ultrasound.

25

2126685

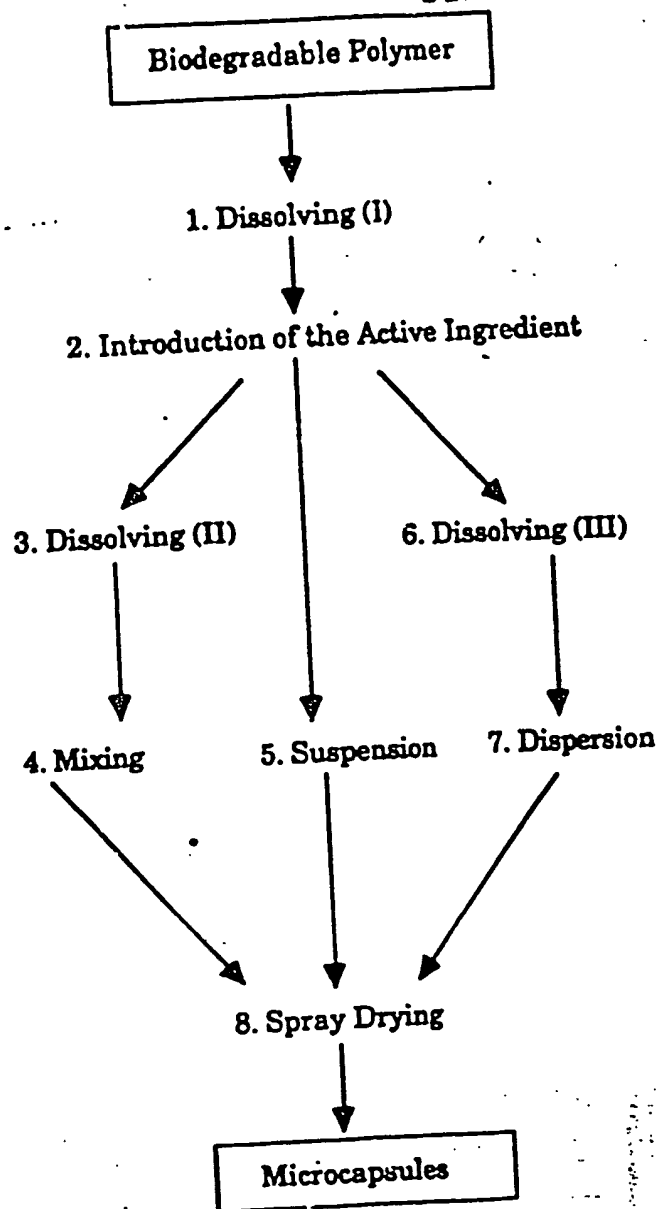


Fig. 1

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☒ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☒ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☒ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.